

# **EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PHENOL**

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## **PHENOL** (CAS No. 108-85-2)

- Molecular formula:  $\text{C}_6\text{H}_5\text{OH}$
- Annual U.S. production over a billion pounds
- Exposure may occur in the workplace, via contaminated environmental media, or through use of consumer products



## PHARMACOKINETICS OF PHENOL

- Absorbed by oral, inhalation, or dermal routes
- Rapid distribution throughout the body
- Metabolism by Phase II conjugation or Phase I oxidation
- Excretion of unchanged phenol or metabolites primarily in urine
- Short half-life: approximately 3.5 hours in humans



# **Non-DART Effects of Phenol**

## **Acute Effects:**

- Severe irritation of skin, eyes and mucous membranes
- Muscle weakness, tremors, loss of coordination, paralysis, convulsions, coma, and death.

## **Chronic Effects:**

- Reductions in feed and water consumption
- Decreased weight gain

## **Carcinogenicity:**

- U.S. EPA “Group D”
- Promoting activity when applied repeatedly to mouse skin



## **Developmental Toxicity of Phenol: Human Data**

*Hernberg, et al., 1983 (abstract)*

No meaningful associations between maternal exposure to disinfectants and the occurrence of congenital defects

*Axelsson, et al., 1984*

Non-significant increase in rate of miscarriage (RR=1.31, 95% confidence interval of 0.89-1.91)



## Developmental Toxicity of Phenol: Animal Data (1)

*RTI, 1983a (rats)*

- Fetal effects at non-maternally toxic doses
- Decreased fetal weights (120 mg/kg)
- Increased litters with resorptions (30, 60 mg/kg)

*RTI, 1983b (mice)*

- Decreased fetal weights (280 mg/kg)
- Maternal mortality and decreased weight (280 mg/kg)

*Argus, 1997 (rats)*

- Decreased fetal weights (360 mg/kg)
- Decreased maternal weight and weight gain (360 mg/kg)



## Developmental Toxicity of Phenol: Animal Data (2)

*Kavlock, 1990 (rats)*

- Kinked tails and limb paralysis (667, 1000 mg/kg)
- Reduced maternal weight gain

*Narotsky & Kavlock, 1995 (rats)*

- Reduced viability (40, 53.3 mg/kg)
- Kinked tails

*U.S. EPA, 1999; Ryan et al., 2001 (rats)*

- Reduced litter weight (5000 ppm)
- Reduced maternal feed and water consumption
- Reduced maternal body weight and weight gain



## Male Reproductive Toxicity of Phenol: Animal Data

*U.S. EPA, 1999; Ryan et al., 2001 (rats)*

- No effect on mating or fertility
- Increased age at preputial separation (5000 ppm)
- Decreased absolute prostate weight (all concentrations)
- Decreased relative prostate weight (1000 ppm)
- Reduced feed and water consumption (5000 ppm)
- Decreased body weights (5000 ppm)

*Bulsiewicz, 1977 (mice)*

- Chromosomal changes in spermatogonia and 1° spermatocytes
- Cell preps from 3 moribund males (640 mg/kg):
  - ✓ No 1° or 2° spermatocytes, spermatids, or spermatozoa
  - ✓ Relative excess of proliferating spermatogonia



## **Female Reproductive Toxicity of Phenol: Human Data**

*Hernberg, et al., 1983 (abstract)*

No meaningful association with occurrence of congenital defects

*Axelsson, et al., 1984*

Non-significant increase in rate of miscarriage (RR=1.31, 95% confidence interval of 0.89-1.91)

*Polish language studies of placental structure and histopathology*

Changes consistent with impairments of placental function



## Female Reproductive Toxicity of Phenol: Animal Data (1)

*U.S. EPA, 1999; Ryan et al., 2001 (rats)*

- Reduced water and feed consumption (5000 ppm)
- Decreased body weight and weight gain (5000 ppm)
- No effects on mating or fertility
- No change in estrous cycle length
- Increased age at vaginal opening (5000 ppm)
- Decreased absolute and relative uterine weights (all concentrations)



## Female Reproductive Toxicity of Phenol: Animal Data (2)

*RTI, 1983a (rats)*

- Excess maternal mortality at doses  $\geq 160$  mg/kg
- Reduced pregnancy rate at doses  $\geq 160$  mg/kg

*RTI, 1983b (mice)*

- Increased maternal mortality (280 mg/kg)
- Decreased maternal weight and weight gain (280 mg/kg)
- No effect on pregnancy rate or live litter size
- Increased resorptions and nonlive fetuses (pilot only)

*Argus, 1997 (rats)*

- No effects on corpora lutea, implantation, resorptions or live litter size
- Effects on maternal weight and weight gain (360 mg/kg)



# Summary of DART Effects Reported Following Phenol Exposure

## Developmental

- Decreased fetal or birth weight
- Decreased fetal viability

## Male Reproductive

- Reduced prostate weights
- Delayed preputial separation
- Increased chromosome aberrations

## Female Reproductive

- Delayed vaginal opening
- Reduced uterine weights





## F1 Body and Uterine Weights

